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(54) Title: USE OF PHOSPHONIC ACID ESTERS FOR THE TREATMENT OF FUNCTIONAL DISORDERS OF THE BRAIN AND DEPRESSION

(57) Abstract

The present invention relates to the use of phosphonic acid esters for the treatment and prevention of functional disorders of the brain and depression.

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Use of phosphonic acid esters for the treatment of functional disorders of the brain and depression

The invention relates to the use of phosphonic acid esters for the treatment and prevention of functional disorders of the brain and depression, and to new compounds and their production.

DE-1 078 370 discloses phosphonic acid esters used for the control of insects.

It is also known that the anthelmintic metrifonate is suitable for the treatment of Alzheimer's disease (US 4,950,658). The assumed mode of action is that metrifonate is converted slowly into the organophosphoric acid ester dichlorvos and ther by induces a long-lasting inhibition of cholinesterase. In the furth r pursuit of this theory butonate was proposed as a suitable precursor for metrifonate/dichlorvos (B R

R^1 represents hydrogen or straight-chain or branched alkyl with up to 6 carbon atoms,

R^2 represents hydrogen or
represents straight-chain or branched alkyl, alkylcarbonyl, alkoxycarbonyl or alkylsulphonyl with in each case up to 6 carbon atoms in the alkyl group, or
represents alkyl- or dialkylaminocarbonyl with in each case up to 4 carbon atoms in the alkyl groups,

R^3 represents straight-chain or branched alkyl with up to 6 carbon atoms

and

X represents oxygen or sulphur,
but does not denote oxygen where R represents trichloromethyl, R^1 represents hydrogen and R^2 represents hydrogen or propylcarbonyl,

and the salts and isomers thereof,

can be used for the treatment and prevention of functional disorders of the brain and depression, even without any conversion into a cholinesterase inhibitor taking place.

The compounds of the formula (I) are suitable for the treatment and prevention of cognitive and affective diseases, and in particular for the treatment of senile and presenile dementia, dementia of the Alzheimer's type, AIDS-related dementia, cognitive deficits in Parkinson's and Huntington's disease or functional disorders of the brain as a result of infarction, multi-infarct dementia (MID), primary degenerative dementia (PDP) and other forms of dementia

and for the tr atment of depression.

They are also suitable for the treatment of functional disorders of the brain in the elderly, organic brain syndrome (OBS) and age-associated memory impairment (AAMI).

The compounds of the general formula (I) are extremely suitable for the treatment and prevention of senile and presenile dementia and dementia of the Alzheimer's type.

The compounds of the formula (I)

in which

R represents straight-chain or branched alkyl with up to 4 carbon atoms or trifluoromethyl, trichloromethyl, difluoromethyl, 1,1-dichloroethyl, dichloromethyl, fluoromethyl, chloromethyl, dichlorofluoromethyl, difluorochloromethyl or represents the radical of the formula $-CCl_2CH_2Cl$, (1,1,2-trichloroethyl),

R^1 represents hydrogen or straight-chain or branched alkyl with up to 4 carbon atoms,

R^2 represents hydrogen or represents straight-chain or branched alkyl, alkylcarbonyl, alkoxycarbonyl or alkylsulphonyl with up to 4 carbon atoms in the alkyl group, or represents alkyl or dialkylaminocarbonyl with in each case up to 3 carbon atoms in the alkyl groups,

R^3 represents straight-chain or branched alkyl with up to 3 carbon atoms

and

X represents oxygen or sulphur,

but does not denot oxyg n where R represents trichloromethyl, R^1 represents hydrogen and R^2 represents hydrogen or propylcarbonyl,

and their salts and isomers are particularly suitable for the treatment and prevention of cognitive and affective disorders.

Compounds of the general formula (I)

in which

R represents methyl, tert.-butyl, 1,1-dichloroethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, dichlorofluormethyl, difluorochloromethyl or the radical $-CCl_2CH_2Cl$, (1,1,2-trichloroethyl)

R^1 represents hydrogen or methyl,

R^2 represents hydrogen, methyl, ethyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl, t-butylcarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert.-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl, methylaminocarbonyl, dimethylaminocarbonyl or propylaminocarbonyl,

R^3 represents methyl, ethyl or propyl,

and

X represents oxygen or sulphur,

but does not denote oxygen where R represents trichloromethyl and R^1 represents hydrogen or propylcarbonyl,

and their salts and isomers are particularly preferred.

The compounds according to the invention can exist in stereoisomeric forms which are either in the form of image and mirror image (enantiomers) or are not in the form of image and mirror image (diastereomers). The invention relates both to the enantiomers and the diastereomers and to respective mixtures thereof. Both the racemic forms and the diastereomers can be separated by the known methods into the stereoisomerically homogeneous components.

The invention also relates to the following compounds:
dimethyl (1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-phosphonate
dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-ethanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-methoxycarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-acetyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-methoxycarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-propylcarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-methanesulphonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-dimethylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-acetyloxy-2,2,2-trichloroethane)-thiophosphonate
dimethyl (1-methoxycarbonyloxy-2,2,2-trichloroethane)-thio-phosphonate,
dimethyl (1-dimethylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate
dimethyl (1-hydroxy-2,2,2-trifluoroethane)-thiophosphonate,

dimethyl (1-propylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate

dimethyl (1-propylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl-(1-ethoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-acetyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (S)-(1-acetyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (R)-(1-hydroxy-2,2,2-trichloroethane)thiophosphonate,

dimethyl (S)-(1-hydroxy-2,2,2-trichloroethane)thiophosphonate,

dimethyl (R)-(1-hydroxy-2,2,2-trifluoroethane)thiophosphonate,

dimethyl (S)-(1-hydroxy-2,2,2-trifluoroethane)thiophosphonate,

dimethyl (R)-(1-ethylcarbonyloxy-2,2,2-trichloroethane)-phosphonate

dimethyl (S)-(1-ethylcarbonyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (2,2-dichloro-1-hydroxypropane)-phosphonate,

dimethyl (1-hydroxy-2,2,3-trichloropropane)-phosphonate,

dimethyl (1-hydroxy-2,2,2-trimethylethane)-phosphonate,

dimethyl (R)-(1-hydroxy-2,2,2-trimethylethane)-phosphonate,

dimethyl (S)-(1-hydroxy-2,2,2-trimethylethane)-phosphonate,

dimethyl (R)-(1-tert.-butylcarb nyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (S)-(1-tert.-butylcarb nyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (R)-(1-meth xycarbonyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (S)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (R)-(1-acetyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-acetyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-methoxycarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-methoxycarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-propylcarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-propylcarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-methanesulphonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-methanesulphonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-dimethylaminocarbonyloxy-2,2,2-trifluoro-ethane)-phosphonate,

dimethyl (S)-(1-dimethylaminocarbonyloxy-2,2,2-trifluoro-ethane)-phosphonate,

dimethyl (R)-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-acetyloxy-2,2,2-trichloroethane)-thio-phosphonate,

dimethyl (S)-(1-acetyloxy-2,2,2-trichlor ethane)-thio-phosphonate,

dimethyl (R)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate

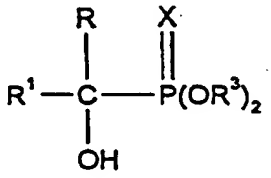
dimethyl (R)-(1-hydroxy-2,2,2-trifluoroethane)-thio-phosphonate,
dimethyl (S)-(1-hydroxy-2,2,2-trifluoroethane)-thio-phosphonate,
dimethyl (R)-(1-propylaminocarbonyloxy-2,2,2-trichloro-ethane)-thiophosphonate,
dimethyl (S)-(1-propylaminocarbonyloxy-2,2,2-trichloro-ethane)-thiophosphonate,
dimethyl (R)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (S)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (R)-(1-propylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (S)-(1-propylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (R)-(1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (S)-(1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (R)-(1-ethoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (S)-(1-ethoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate.

The present invention also relates to the use of the following compounds which are already known:

	Literature
dimethyl (1-acetyloxy-2,2,2-trichloroethane)-phosphonate,	1
dimethyl 1-hydroxyethanephosphonate,	2
dimethyl (R)-(1-hydroxyethane)-ph sphonate,	3
dimethyl (S)-(1-hydroxy thane)-ph sphonate,	3
dimethyl (1-hydroxy-2,2,2-trichloroethane)thiophosphonate,	4
dimethyl (1-ethylcarbonyloxy-2,2,2-trichloroethane)-ph sphonate,	1

The new and known compounds of the formula (I) used according to the invention are prepar d by reacting

1-hydroxy-phosphonic acid esters of the formula (II)



(II)

in a known manner with halogen compounds of the formula (III)

$$Hal\text{-}R^2 \qquad (III)$$

optionally in the presence of acid-binding agents or optionally in the form of their alkali metal, alkaline earth metal or ammonium salts and optionally in the presence of solvents, or, where R^2 represents alkylcarbonyl, alternatively with carboxylic anhydrides of the formula (IV)

$$R^2\text{-}O\text{-}R^2 \qquad (IV)$$

optionally in the presence of catalytic amounts of a mineral acid,

and in the case of the enantiomerically pure hydroxyl compounds the racemates are separated by column chromatography by the method described in WO 93/24130 or by other known methods

and in the case of the acylated compounds the hydroxyl compounds which are already enantiomerically pure are used.

The starting compounds of the formulae (II), (III) and (IV) are known or can be prepared by known methods.

The process for the preparation of the compounds of the formula (I) by reaction with the halogen compounds of the formula (III) is preferably carried out using diluents. Suitable diluents are virtually all inert organic solvents. These preferably include aliphatic and aromatic, optionally halogenated hydrocarbons such as pentane, hexane, heptane, cyclohexane, petroleum ether, benzine, ligroin, benzene, toluene, xylene, methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene and o-dichlorobenzene, ethers such as diethyl and dibutyl ether, glycol dimethyl ether and diglycol dimethyl ether, tetrahydrofuran and dioxan, ketones such as acetone, methyl thyl, methyl isopropyl and methyl isobutyl ketone, esters such as methyl and ethyl acetate, nitriles, such as for example acetonitrile and propionitrile, amides such as for example dimethyl formamide, dimethyl acetamide and N-methylpyrrolidone as well as dimethyl sulphoxide, tetramethylene sulphone and hexamethylphosphoric triamide.

Those acid-binding agents which can usually be employed for such reactions can be us d as acid acceptors. Alkali metal and alkaline earth m tal hydrides such as lithium, sodium, potassium and calcium hydride, alkali metal and alkaline earth

and 5-ethyl-2-methylpyridine, 1,5-diazabicyclo-[4,3,0]-non-5-ene (DBN), 1,8-diazabicyclo-[5,4,0]und c-7-ene (DBU) and 1,4-diazabicyclo-[2,2,2]-octane (DABCO) are preferably usable.

The reaction temperatures can be varied over a relatively large range. In general temperatures of between 0°C and 100°C, and preferably temperatures of between 10°C and 80°C are used.

The process is generally carried out under normal pressure. It is however also possible to use increased or reduced pressure.

When carrying out the process the starting materials required in each case are generally used in approximately equimolar quantities. It is however also possible to use one of the two components employed in each case in a relatively large excess. The reaction is generally carried out in a suitable diluent in the presence of an acid acceptor and the reaction mixture is stirred for several hours at the temperature required in each case. The working up process is carried out in each case by the usual methods (cf. the preparation examples).

The process for the preparation of the compounds (I) by reaction with the carboxylic anhydrides of the formula (IV) can also be carried out without diluents. All the usual mineral acids can be used as the catalyst. Preferred acids are sulphuric acid, hydrochloric acid or phosphoric acid. They are used in a quantity of 0.001 to 10 mol %.

The compounds are usually obtained in the form of oils which in some cases cannot be distilled without decomposition, but which can be fre d from the residual volatile constituents by so-call d "incipient" distillation, i.e. by heating the compounds at moderately increased temperatures for relatively

1 ng periods under reduced pressure, as a r sult of which they are purifi d. The compounds are characterised by means of their refractiv index. The crystalline compounds are characterised by their melting point.

The activity of the phosphonic acid esters for the treatment and prevention of cognitive disorders is demonstrated by means of an animal experiment based on spatial memory. In this test, which was originally described by Morris (R.G.M. Morris, J. Neurosci. Methods 11:47-60, 1984), rats have to learn how to localise a platform which they cannot see but which is the only way out of a pool filled with water. For this purpose the animals (young, adult, male, approximately 3-month-old rats) undergo 4 training cycles per day over a period of 3 days. The latent period before the rats discover the platform and the distance covered are determined. During the course of the training not only the latent period but also the distance swum becomes shorter as a result of the rats' adoption of a strategy for spatially localising the destination. The cognition-improving activity of the test substances is manifested by a shortening of the time required for the learning process, i.e. the learning curve becomes steeper. Test substances are administered once daily (60 mins. before the first training cycle). Control animals are administered a corresponding amount of the vehicle.

At the end of the training phase, i.e. after the end of the 12th training cycle the platform is removed from the water and an additional swimming test is carried out in order to examine whether the test animals look for the platform within a defined small area surrounding the training position of the platform (retention test).

The activity of some compounds in relation to learning and remembrance processes were examined in the "Active Avoidance Test". In this aversion-motivated test rats have to learn to

move to the other side of a shuttle box consisting of two compartments (Coulbourn Instruments) as soon as a conditioned stimulus is actuated. The conditioned stimulus consists of the simultaneous sounding of an acoustic signal and the flashing of a small light. If the rat does not leave the compartment of the shuttle box within 6 seconds after the onset of the stimulus it is given a slight electric shock (0.5 mA) via the base grid of the shuttle box. The acquisition of the active avoidance behaviour is recorded over 20 conditioning tests on each of two successive days. The individual tests are separated from each other by variable breaks of 20 to 60 seconds. The increase in the correct avoidance reactions during the course of the training is used as a criterion for the learning activity of the animals.

In order to record the effects of substances on memory performance adult male rats are treated with test substances 30 minutes before the first test; the control animals are administered a corresponding amount of the vehicle.

The test results show that the abovementioned compounds have a positive effect on the learning behaviour of the animals and the retention of what has been learned. The special advantage of the abovementioned compounds is that they do not induce any inhibition of cholinesterase activity in the brain within their active dosage range. This results in improved tolerance compared with procholinergic reference substances; such as for example tetrahydroaminoacridine, physostigmine or metrifonate. The abovementioned phosphonic acid esters can therefore be used both for the therapeutic and the preventive treatment of cognitive disorders in general, and in particular dementias of the Alzheimer's type.

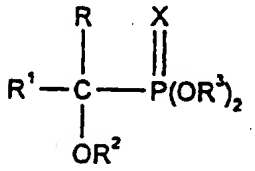
The activity of the phosphonic acid esters for the treatment and prevention of affective disorders is demonstrated with the aid of the "Rat Forced Swimming Test". This behavioural model was described for the first time by Porsolt et al. (R.D.

Porsolt, M. Le Pichon, M. Jalfre, Nature 266:730-732, 1977) and is today a widely accepted in vivo scr ening mod l for detecting new antidepressants. It is based on the finding that rats remain in a motionless state in a desperate situation ("behavioural despair"). In a preliminary test young, adult (3-4-month-old) rats are placed individually in glass cylinders (40 cm in height and 20 cm in diameter) which are filled with water up to a level of 15 cm, for 20 minutes. 24 hours after this preliminary test the animals are again placed in the cylinders and the duration of their immobility is determined over a period of 5 minutes. The abovementioned phosphonic acid esters are administered in the interval between the two swimming tests. The control animals are administered the vehicle.

Similarly to the clinically active antidepressants described in the literature the abovementioned phosphonic acid esters shorten the duration of immobility and result in behavioural activation. By reason of these results the abovementioned compounds are also suitable for the treatment of affective disorders, and in particular depression.

As with the cognition-improving activity this antidepressive component can also not be explained by the inhibition of cholinesterase.

Biological data on:



(I)

R^1	R	R^2	R^3	X		ED_{50} oral admin. Rat Forced SwimTest	active doses oral admin. Morris Maze (MM) Active Avoidance (AA)
-H	$-CCl_3$	-H	$-CH_3$	O	metrifonate (reference)	2.3 mg/kg	MM 10-30 mg/kg AA 12.5-25 mg/kg
-H	$-CCl_3$	$-COC_3H_7$-n	$-CH_3$	O	butonate (reference)	1.7 mg/kg	MM 1-3 mg/kg
-H	$-CCl_3$	$-SO_2-CH_3$	$-CH_3$	O		4.3 mg/kg	MM 3 mg/kg
-H	$-CCl_3$	$-COCH_3$	$-CH_3$	O		0.03 mg/kg	MM 0.03-0.1 mg/kg
-H	$-CH_3$	-H	$-CH_3$	O		0.8 mg/kg	MM 3 mg/kg
-H	$-CCl_3$	-H	$-CH_3$	S		0.9 mg/kg	AA 1-3 mg/kg
-H	$-CCl_3$	$-SO_2-CH_3$	$-CH_3$	S		2.1 mg/kg	AA 5-10 mg/kg
-H	$-CCl_3$	$-COCH_3$	$-CH_3$	S		0.05 mg/kg	AA 0.05 mg/kg

The activity of dimethyl(1-hydroxy-2,2,2-trimethylethane)-phosphonate and its enantiomers can be tested by the following experiment:

6-8-week old ICR mice (weighing approx. 22-28 g) from Harlan-Sprague-Dawley, Inc. (Indianapolis Indiana, USA) were used for this test. 8 animals at a time were placed together in a cage; they had free access to feed and water.

The Morris Maze consisted of a circular, galvanised steel tank which was painted white (and was open at the top) and had a diameter of 76 cm; at the base of the tank a plastic holding device for the attachment of the exit platform was arranged in each of 4 identically sized circular segments. Prior to the behavioural test the tank was filled with water to such a level that the 25 cm high platform was 1 cm bel w the surface f the water; the water had been preheated to 22°C and

After one week's acclimatisation in animal housing the mice had the opportunity to swim freely in the abovementioned steel tank (no platform present) for 90 seconds. One to three days later the acquisition training began which consisted of 4 cycles on each of three successive days (a total of 12 cycles). No test substances were administered. The allocation of the mice to the target quadrants, in each of which the platforms were arranged was based on random selection. The mice were placed in the water facing the wall of the tank at one of 4 points uniformly distributed around the circumference of the Morris Maze; the starting position varied per mouse from one cycle to the next in such a manner that each mouse started from each of the four starting points once a day. In each of the training cycles the mice had a period of 120 seconds to reach the target platform. If they did not do so within this period they were placed on the target platform by hand. There was an interval of 30 seconds, in which the mouse remained on the target platform, between each cycle.

On the fourth day the behaviour of the animals was examined for 30 seconds in a trial cycle in which no platform was present; the period f time which the mice spent in each of the f ur quadrants was determined. The mice had been administered the substance t be tested or the vehicle 30 minutes or one hour before the test cycle; the selection of mice for the vehicle and test substance groups was carried ut at

excipients or solvents. The therapeutically active compound should b used in each cas in a concentration of approximately 0.5 to 90% by weight of the total mixture, i.e. in quantities which are sufficient to obtain the indicated dosage range.

The formulations are for example prepared by extending the active compounds with solvents and/or excipients, optionally using emulsifiers and/or dispersants, it being possible optionally to use organic solvents as auxiliary solvents where water is for example used as a diluent.

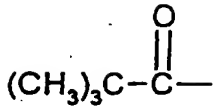
Administration is carried out in the usual manner, preferably orally or parenterally, and in particular perlingually or intravenously. Administration can also be carried out transdermally, such as for example by means of plasters.

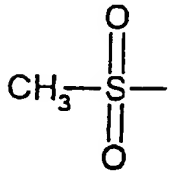
In the case of parenteral administration solutions of the active compound can be employed using suitable liquid excipient materials.

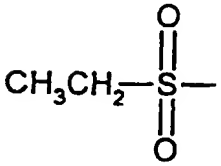
In the case of intravenous administration it has in general proven advantageous to administer quantities of approximately 0.001 to 1 mg/kg, preferably approximately 0.01 to 0.5 mg/kg of body weight for the obtainment of effective results and in the case of oral administration the dosage is approximately 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

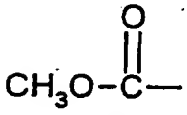
It may nevertheless possibly be necessary to deviate from the abovementioned quantities depending on the body weight involved and the type of administration employed, on the individual response to the medicament, and the type of formulation used and the time or interval at which it is administered. Thus it can in some cases be sufficient to use less than the abovementioned minimum quantity, whereas in other cases th abovementioned upp r limit must be exceeded. Where larger quantities are used it can be recommendable to distribute them over several individual doses per day.

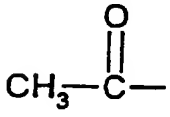
Abbreviations used:

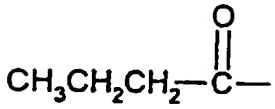
Piv = 

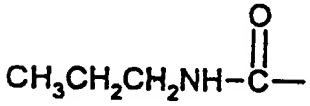
Ms = 

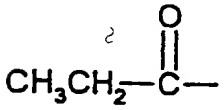
Es = 

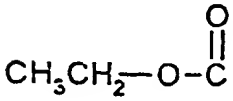
Moc = 

Ac = 

Butyryl = 

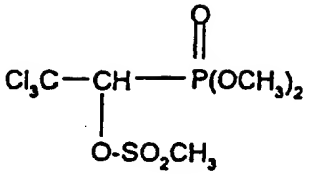
CONHPr = 

Propionyl = 

Eoc = 

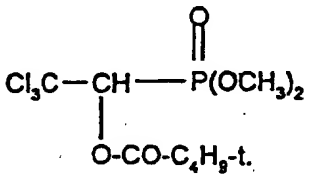
Preparation examples

Example 1



6.3 g (0.055 mol) of methanesulphonic acid chloride are added dropwise with cooling at 5°C to a mixture of 12.87 g (0.05 mol) of dimethyl (1-hydroxy-2,2,2-trichloroethane)-phosphonate, 6 g (0.06 mol) of triethylamine and 100 ml of methylene chloride and the mixture is then subsequently stirred for 18 hours at room temperature. The reaction mixture is extracted twice, each time with 30 ml of water. The organic phase is separated off, dried over sodium sulphate and freed from the solvent in vacuo. 14.5 g (86 % of theory) of dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-phosphonate remain in the form of colourless crystals with a melting point of 74 to 75°C.

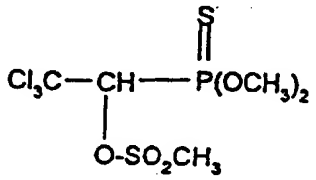
Example 2



A mixture of 13 g of (0.05 mol) of dimethyl (1-hydroxy-2,2,2-trichloroethane)-phosphonate, 60 ml of toluene, 9.5 g (0.05 mol) of pivalic anhydride and 0.05 g of conc. sulphuric acid is stirred for 15 hours at 40°C. Then 50 ml of a saturated sodium bicarbonate solution are added and stirring is continued until the evolution of CO_2 ceases. The organic phase is separated off, dried over

sodium sulphate and concentrated in vacuo. The residue is chromatographed over silica gel (eluent: petroleum ether/acetone 7:3). 6.85 g (40 % of theory) of dimethyl (1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-phosphonate are obtained in the form of a colourless oil with a refractive index $n_D^{20} = 1.4655$.

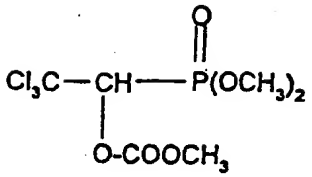
Example 3



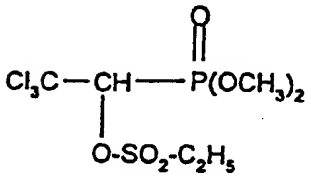
2.3 g (0.02 mol) of methanesulphonic acid chloride are added dropwise with cooling at 5°C to a mixture of 5.5 g (0.02 mol) of dimethyl (1-hydroxy-2,2,2-trichloroethane)-thiophosphonate, 2.5 g (0.025 mol) of triethylamine and 30 ml of diethyl ether and the mixture is then subsequently stirred for 3 hours at room temperature. The reaction mixture is extracted twice, each time with 20 ml of water. The organic phase is separated off, dried over sodium sulphate and freed from the solvent in vacuo. 6.5 g (92 % of theory) of dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate remain in the form of colourless crystals with a melting point of 47.5 to 50.5°C.

The following compounds can be prepared analogously to one of examples 1 to 3:

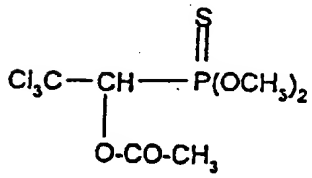
Example 4



Example 5

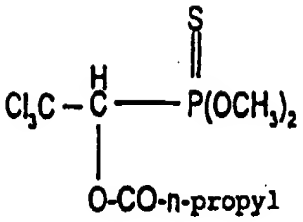


Example 6



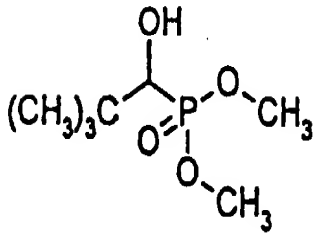
$n_D^{20} = 1.5101$

Example 7



$n_D^{20} = 1.4958$

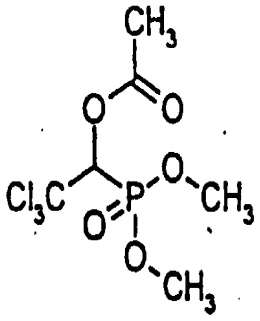
Example 8



1 mol of triethylamine is added to 1.05 mols of pivalic aldehyde and 1 mol of dimethyl phosphite while cooling with ice. The mixture is stirred overnight at 25°C and then concentrated. The residue is kept at 40°C overnight under high vacuum.

n_{20}^{D} 1,4485

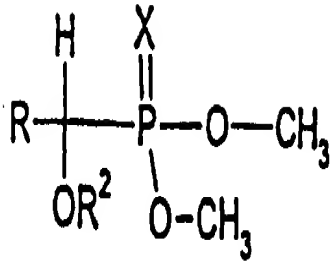
Examples 9 and 10



enantiomer

1 ml of conc. sulphuric acid was added to 1 mol of enantiomerically pure dimethyl (1-hydroxy-2,2,2-trichloroethane)-phosphonate in 1 l of acetic anhydride and the mixture was heated for 2 hours at 90°C. The

Table 1:



Example No.	R	R^2	X	configuration
11	CCl_3	Piv	O	R
12	CCl_3	Piv	O	S
13	CCl_3	Ms	O	R
14	CCl_3	Ms	O	S
15	CCl_3	Es	O	R
16	CCl_3	Es	O	S
17	CCl_3	M c	O	R
18	CCl_3	M c	O	S
19	CF_3	Ac	O	R
20	CF_3	Ac	O	S
21	CF_3			

Example No.	R	R^2	X	configuration
38	CCl_3	Ac	S	S
39	CCl_3	Moc	S	R/S
40	CCl_3	Moc	S	R
41	CCl_3	Moc	S	S
42	CCl_3	$CONMe_2$	S	R/S
43	CCl_3	$CONMe_2$	S	R
44	CCl_3	$CONMe_2$	S	S
45	CF_3	H	S	R/S
46	CF_3	H	S	R
47	CF_3	H	S	S
48	CCl_3	CONHPr	S	R/S
49	CCl_3	CONHPr	S	R
50	CCl_3	CONHPr	S	S
51	CCl_3	Ms	S	R
52	CCl_3	Ms	S	S
53	CCl_3	Butyryl	S	R
54	CCl_3	Butyryl	S	S
55	CCl_3	Piv	S	R/S
56	CCl_3	Piv	S	R
57	CCl_3	Piv	S	S
58	CCl_3	Eoc	S	R/S
59	CCl_3	Eoc	S	R
60	CCl_3	Eoc	S	S
61	CCl_3			

Literature

1 Dakl. Bolg. Akad. Nauk. 1979, 32, 1357 - 1360

2 Sbornik Statei Obshchei Khim., Akad. Nauk. S.S.S.R. 1953, 1, 393 - 397

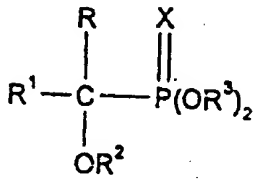
3 Tetrahedron: Assymetry 1993, 4, 109 - 120

4 DE 2 512 375

5 J. Chem. Soc. Perkin Trans. 1, 1994, 1180

Claims

1. **Compounds** of the general formula



(I)

in which

R represents straight-chain or branched alkyl which has up to 6 carbon atoms and is optionally substituted by one or more halogen atoms,

R^1 represents hydrogen or straight-chain or branched alkyl with up to 6 carbon atoms,

R^2 represents hydrogen or
represents straight-chain or branched alkyl, alkylcarbonyl, alkoxycarbonyl or alkylsulphonyl with in each case up to 6 carbon atoms in the alkyl group, or
represents alkyl- or dialkylaminocarbonyl with in each case up to 4 carbon atoms in the alkyl groups,

R^3 **represents** straight-chain or branched alkyl with up to 6 carbon atoms, **and can be identical or different,**

and

X represents oxygen or sulphur,
but do s not denote oxygen where R represents trichloromethyl, R^1 represents hydrogen and
R^2 represents hydrogen or propylcarbonyl,

and their salts and isomers,

for therapeutic use.

2. Compounds according to Claim 1, wherein

R represents straight-chain or branched alkyl with up to 4 carbon atoms or trifluoromethyl, trichloromethyl, difluoromethyl, 1,1-dichloroethyl, dichloromethyl, fluoromethyl, chloromethyl, dichlorofluoromethyl, difluorochloromethyl or represents the radical of the formula $-CCl_2CH_2Cl$, (1,1,2-trichloroethyl),

R^1 represents hydrogen or straight-chain or branched alkyl with up to 4 carbon atoms,

R^2 represents hydrogen or represents straight-chain or branched alkyl, alkylcarbonyl, alkoxycarbonyl or alkylsulphonyl with up to 4 carbon atoms in the alkyl group, or represents alkyl or dialkylaminocarbonyl with in each case up to 3 carbon atoms in the alkyl groups,

R^3 represents straight-chain or branched alkyl with up to 3 carbon atoms, and can be identical or different,

and

X represents oxygen or sulphur,

but does not denote oxygen where R represents trichloromethyl, R^1 represents hydrogen and R^2 represents hydrogen or propylcarbonyl,

and their salts and isomers,

for therapeutic use.

3. Compounds according to Claim 1, wherein

R represents methyl, tert.-butyl, 1,1-dichloroethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoromethyl, dichlorofluormethyl, difluorochloromethyl or the radical $-CCl_2CH_2Cl$, (1,1,2-trichloroethyl),

R^1 represents hydrogen or methyl,

R^2 represents hydrogen, methyl, ethyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl, tert.-butylcarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert.-butoxycarbonyl, methylsulphonyl, ethylsulphonyl, propylsulphonyl, methylaminocarbonyl, dimethylaminocarbonyl or propylaminocarbonyl,

R^3 represents methyl, ethyl or propyl,

and

X represents oxygen or sulphur, but does not denote oxygen where R represents trichloromethyl and R^1 represents hydrogen or propylcarbonyl,

and their salts and isomers,

for therapeutic use.

4. Compounds according to any of claims 1 to 3, wherein

R represents methyl, trifluoromethyl or tert.-butyl,

R^1 represents hydrogen or methyl,

R^2 represents hydrogen,

R^3 represents methyl

and

X represents oxygen,

and their salts and isomers,

for therapeutic use.

5. Medicaments containing at least one phosphonic acid ester according to claim 1 to 4 as well as suitable formulation auxiliaries.

6. Medicaments according to claim 5 for the treatment and prevention of functional disorders of the brain and depression.

7. Use of compounds according to claim 1 to 4 for the preparation of medicaments.

8. Use of compounds according to claim 1 to 4 for the preparation of medicaments for the treatment and prevention of functional disorders of the brain and depression.

9. Compounds of the general formula (I),

selected from the following:

dimethyl (1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-phosphonate
dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-ethanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,

dimethyl (1-methoxycarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-acetyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-methoxycarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-propylcarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-methanesulphonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-dimethylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (1-acetyloxy-2,2,2-trichloroethane)-thiophosphonate
dimethyl (1-methoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (1-dimethylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate
dimethyl (1-hydroxy-2,2,2-trifluoroethane)-thiophosphonate,
dimethyl (1-propylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate
dimethyl (1-propylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl-(1-ethoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,
dimethyl (R)-(1-acetyl xy-2,2,2-trichloroethane)-ph sphonate,
dimethyl (S)-(1-acetyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (R)-(1-hydr xy-2,2,2-trichl roethane)thioph sphonate,
dimethyl (S)-(1-hydroxy-2,2,2-trichl roethane)thiophosphonate,
dimethyl (R)-(1-hydroxy-2,2,2-trifl oethane)thiophosphonate,

dimethyl (S)-(1-ethylcarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (2,2-dichloro-1-hydroxypropane)-phosphonate,
dimethyl (1-hydroxy-2,2,3-trichloropropane)-phosphonate,
dimethyl (1-hydroxy-2,2,2-trimethylethane)-phosphonate,
dimethyl (R)-(1-hydroxy-2,2,2-trimethylethane)-phosphonate,
dimethyl (S)-(1-hydroxy-2,2,2-trimethylethane)-phosphonate,
dimethyl (R)-(1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (S)-(1-tert.-butylcarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (R)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (S)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (R)-(1-ethanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (S)-(1-ethanesulphonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (R)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (S)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (R)-(1-acetyloxy-2,2,2-trifluor ethane)-phosph nate,
dimethyl (S)-(1-acetyloxy-2,2,2-trifluoroethane)-phosphonate,
dimethyl (R)-(1-meth xycarb nyloxy-2,2,2-trifluor ethane)-phosphonate,
dimethyl (S)-(1-methoxycarbonyloxy-2,2,2-trifluoroethane)-phosphonate

dimethyl (S)-(1-dimethylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (S)-(1-propylaminocarbonyloxy-2,2,2-trifluoroethane)-phosphonate,

dimethyl (R)-(1-acetyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (S)-(1-acetyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (S)-(1-methoxycarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-dimethylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (S)-(1-dimethylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-hydroxy-2,2,2-trifluoroethane)-thiophosphonate,

dimethyl (S)-(1-hydroxy-2,2,2-trifluoroethane)-thiophosphonate,

dimethyl (R)-(1-propylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (S)-(1-propylaminocarbonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-thi phosphonate,

dimethyl (S)-(1-methanesulphonyloxy-2,2,2-trichloroethane)-thiophosphonate,

dimethyl (R)-(1-propylcarbonyloxy-2,2,2-trichloroethane)-

10. Compounds of the general formula (I),

selected from the following:

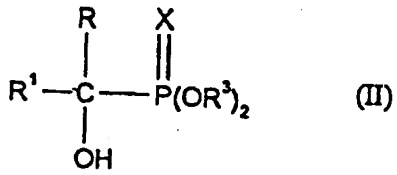
dimethyl (1-acetyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl 1-hydroxyethanephosphonate,
dimethyl (R)-(1-hydroxyethane)-phosphonate,
dimethyl (S)-(1-hydroxyethane)-phosphonate,
dimethyl (1-hydroxy-2,2,2-trifluoroethane)phosphonate,
dimethyl (1-hydroxy-2,2,2-trichloroethane)thiophosphonate,
dimethyl (1-ethylcarbonyloxy-2,2,2-trichloroethane)-phosphonate,
dimethyl (1-hydroxy-1-methylethane)-phosphonate.

for therapeutic use.

11. Process for the preparation of phosphonic acid esters according to claims 1, 2, 3, 4, 9 or 10,

characterised in that

1-hydroxy-phosphonic acid esters of the formula (II)



(II)

are reacted in a known manner with halogen compounds of the formula (III)

$$Hal\text{-}R^2 \qquad (III)$$

optionally in the presence of acid-binding agents or optionally in the form of their alkali metal, alkalin earth metal or ammonium salts and optionally in the presence of solvents, or, where R^2 represents alkylcarbonyl, alternatively

with carboxylic anhydrides of the formula (IV)

$$R^2\text{-}O\text{-}R^2 \qquad (IV)$$

optionally in the presence of catalytic amounts of a mineral acid.

12. Process according to claim 11, characterised in that basic nitrogen compounds are used as the acid-binding agents.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 97/06469

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/66 C07F9/40 //C07M7:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 950 658 A (ROBERT E. BECKER) 21 August 1990 cited in the application see the whole document ---	1-8, 10-12
Y	HOLMSTEDT B R ET AL: "TOXICOLOGICAL LIMITATIONS TO CHOLINOMIMETIC THERAPY." , BECKER, R. AND E. GIACOBINI (ED.). ADVANCES IN ALZHEIMER DISEASE THERAPY SERIES: CHOLINERGIC BASIS FOR ALZHEIMER THERAPY. X+494P. BIRKHAEUSER BOSTON: CAMBRIDGE, MASSACHUSETTS, USA;BASEL, SWITZERLAND. ILLUS. 0 (0). 1991. 155-161. ISBN: 0-8176-3566-1; XP002034906 cited in the application see page 155-162 --- -/--	1-8, 10-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 1997	21-07-1997

Name and mailing address of the ISA	Authorized officer
European Patent ffice, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Beslier, L

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Inter nal Application No
PCT/US 97/06469

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